

# Understanding Nicotine Addiction: Dependency as a Result of Maladaptive Brain Structure

by Nate Thomas

Nicotine addiction is the most prevalent, destructive dependency found in our culture. Despite its well-documented damaging health risks, nicotine use is still widely accepted and could be conceptualized as a social epidemic. Much of this acceptance may stem from nicotine's lack of debilitating cognitive effects, as compared to those of other abused drugs. However, what may reign dominantly over nicotine's legality is simple cultural precedent: tobacco has never been illegal and holds a place in human history. Therefore, attempting to alter this would prove highly unpopular and unsuccessful. This macroscopic irrationality, a blind favor for cultural precedents, parallels the irrational behaviors exhibited in an individual experiencing nicotine dependence. Just as the dependent brain unconditionally craves nicotine, our culture accepts longstanding practices and traditions, despite the contradictory state they may force upon our laws.

Humans have an extraordinary capacity for rational thought. Therefore it is expected that a rational being be capable of recognizing the dangers of chronic smoking, as this information is widely available in our society, and cease the behavior. This contradiction of logical thought is indicative of the existence of another, more relevant variable in the cultural summation of mass addiction. It is surmisable that this missing variable is the dependent individual's maladaptive brain structure, resulting from genetics, epigenetics, and drug use.

When examining the validity of this claim, it is important to consider a variety of factors that influence the construction of an individual's brain. Genetics can provide a backdrop for the development of dependency. Impulsivity, for example, is a trait resulting from certain genetic coding that may be correlated with drug-seeking behaviors. Additionally, epigenetic processes can lead to heritable reorganization of genetic material and the subsequent synthesis of proteins that expedite and exacerbate the condition of addiction. Just as behavior can alter gene expression, there are more direct mechanisms through which behavior can influence brain

structure. Simply exposing one's nicotinic acetylcholine receptors to nicotine causes immediate and progressive physiological changes, reinforcing the addictive behaviors that cause them. However, even in light of these considerable factors that support the concept of structural dependency, it is important to examine other perspectives. A variety of critiques exist on the validity of the research methods relating to specific brain function that suggest that this data may err on the side of anecdotal evidence, which should be taken into consideration in order to develop a full understanding of this issue.

With the supposition that nicotine addiction is a disease based in maladaptive brain structure, the specific mechanisms involved in this phenomenon must be examined. Before an individual has the opportunity to interact with their environment, genetic diathesis can act as somewhat of a predetermining force in the potential development of nicotine addiction. With the level of technological advancement today, correlational data between genes and behaviors is becoming increasingly available. The NCAM1-TTC12-ANKK1-DRD2 gene cluster located on chromosome 11q23 has been shown to be connected to nicotine dependence later on in an individual's life. The TTC12-ANKK1-DRD2 portion of the gene cluster is specifically associated with impulsivity and nicotine use in adolescence (Wang, Liu, Zhang, and Zeng, 327). This finding is paramount in determining the probability of later nicotine dependence. An adolescent's brain is still acutely developing, and chronic nicotine exposure causes the brain to develop as if nicotine were another neurotransmitter. The brain, in its natural plasticity accepts this artificial chemical stimulation and, in a sense, expects continued stimulation in this manner. This structurally critical period for addiction vulnerability, along with the genetic coding for impulsive behavior, creates an individual primed by their biology to develop an addiction. Yet this presents a question: through what mechanism can genetics change a reaction to nicotine?

The tobacco plant, as a result of natural selection, developed nicotine as a toxic defense mechanism from insects and smaller animals. Today, tobacco persists because of artificial selection, the process describing human involvement in natural selection. Nicotine is capable of binding to nicotinic acetylcholine receptors (shortened to nAChRs), so named for nicotine's affinity for them. These receptors exist in the peripheral nervous system at neuromuscular junctions allowing voluntary muscle contraction, and

in the central nervous system as a part of reward, arousal, and memory processing. A higher concentration of nAChRs in the synapses of neurons increases sensitivity to nicotine, and in turn the likelihood to experience dependence as an eventual result of exposure (Rahman, 352). Neurotransmitter receptors, including nAChRs, are protein molecules fixed into the structure of a synapse between two neurons, and the synthesis of these protein molecules is coded in DNA. Thus, the connection between nicotine sensitivity and genetic coding is obvious: genetic makeup dictates the synthesis of nAChRs, and the concentrations of nAChRs dictates sensitivity to nicotine. This variable sensitivity between individuals results in differing probabilities to experience dependency as a result of exposure to nicotine. However, yet another more complex mechanism is at the root of the heritability and persistence of the brain changes incurred through chronic nicotine use.

A relatively new field of study, epigenetics has resulted in some sweeping changes in the understanding of the interaction of behavior and gene expression. Once perceived as a stable trait throughout the lifespan, genetic makeup is now known to be subject to change over time. These changes result from behavioral factors that affect the expression of genes, causing them to become either active or inhibited. On a structural level, these alterations occur at the histone, the protein formation that DNA winds around (Wong, Mill, and Fernandes, 481). Histone acetylation occurs when a compound derived from acetic acid, an acetyl group, is added to a histone tail, negating its positive charge and causing gene activation (Robison and Nestler, 629). Conversely, methylation occurs when a methyl group, a methane-derived compound, is added to the cytosine base of a DNA molecule, causing chromatin to be condensed and a gene to be silenced (Wong, Mill, and Fernandes, 481). These processes can be caused by the abuse of physically addictive substances, including nicotine (Bilinski, Wojtyła, Kapka-Skryzpzak and Chewedorowicz, 493). This modification of genetic material is one of the most profound changes brought about by chronic drug use, being both heritable in future generations and relatively persistent throughout lifespan.

The processes of acetylation and methylation, in altering gene expression, alter the proteins synthesized in the body. Proteins serve a wide range of functions, including forming some structural aspects of the brain. An example of the persistent changes caused by these epigenetic processes is

the synthesis of the FOSB protein. Synthesis of the FOSB protein, encoded by the FosB gene in the nucleus accumbens, dorsal striatum, and other reward centers of the brain, increases as a result of nicotine use. One of the functions of this protein is to regulate sensitivity of these brain areas to the rewarding aspects of drugs of abuse (Renthal and Nestler, 341). FOS-Bis a truncated version of the FOSB protein that, because of its shortened length, is four times as stable as the normally synthesized protein (Renthal and Nestler, 348). This stability causes the behavioral deviations it creates to be highly persistent, even after nicotine cessation, as the protein remains active in the brain's motivational systems. These long-standing changes indicate that irrational, addictive behaviors are, at their root, a result of maladaptive brain structure.

While epigenetic processes cause persistent alterations over a course of chronic abuse, there are other mechanisms that cause acute brain changes as a result of severe exposure. As opposed to the complex epigenetic mechanisms involved in drug addiction, drug induced structural alterations of the brain are more direct and intuitive changes, acting directly on the receptors to which the drug binds. Exposure to nicotine causes upregulation (an increase in abundance) of the  $\alpha 4\beta 2$  subtype of nicotinic acetylcholine receptors (Govind, Vezina, and Green, 757). This partially explains craving behaviors caused by nicotine use, as the brain seeks to activate these newly formed receptors. While this would also seem to imply an increase in sensitivity as the addiction progresses, another simultaneous mechanism compensates for this. In addition to upregulation, nicotine exposure causes desensitization of the same  $\alpha 4\beta 2$  subtype of nAChRs, making them less responsive to all forms of stimulation (Govind, Vezina, and Green, 758). This phenomenon is more commonly known as tolerance. As the brain experiences upregulation of nAChRs, it craves to have them activated while experiencing a diminished reward as a result of desensitization. This diminished reward system activation, in those prone to addiction, can result in increased administration as well as administration at higher dosages to circumvent a reduction in perceived effect. Behaviors with their roots in dysfunctional brain structure can quickly spawn a physical dependence as these processes cause consumption to spiral out of control. Thus, when attempting to stop consumption, the aversive effects involved with the cessation of nicotine, known as withdrawal symptoms, pose significant challenges.

Withdrawal symptoms, a phenomenon isolated to physically addictive drugs of abuse, are the most common and outwardly visible indication of the genesis of dependence. These effects of chronic substance abuse vary in severity, depending on the drug involved, from simple mood and concentration disturbances to life threatening health complications. Nicotine withdrawal is markedly unpleasant, causing symptoms of irritability, anxiety, and depression. However, these factors are placated by the lack of a life-endangering component in the cessation of smoking. Despite the relative safety of nicotine withdrawal, it is the preventative force in the efforts of many seeking to cease smoking behaviors. In the absence of nicotine, the dependent brain experiences withdrawal symptoms until either enough time is allotted for the brain to naturally down-regulate and re-sensitize the afflicted nAChRs, or the individual consumes more nicotine (Ortells and Barrantes, 889). The latter option is a much more common response as this behavior is supported by a plethora of other aforementioned structural factors. Furthermore the relief it provides is instant, which enforces the mental association of reprieve from negative mood states and nicotine administering behaviors, thereby strengthening the addiction. With these concepts in mind, it becomes clear that withdrawal symptoms are a structurally-based phenomenon, the result of the physical processes of upregulation and desensitization. However, from a different perspective, chronic addictive behaviors stem from the rewiring of the brain's reward system. Closely tied to the function of this motivational system is the neurotransmitter, dopamine.

Dopamine release has long been understood to be involved in the consumption of abused drugs. This neurotransmitter is associated with physically rewarding stimuli, encouraging the consumption of high fat foods and the procreation of our species. In the context of drug use, dopamine reinforces addictive behaviors by activating the same brain circuits designed to motivate an individual to eat and reproduce. Nicotine's rewarding effects stem from activation of the mesocorticolimbic dopamine system, which projects to the nucleus accumbens and other areas of the forebrain. Dopamine release in the nucleus accumbens is present universally in physically addictive substances, demonstrating a strong correlation between this activation and addiction. Defying the intuitive implications of dopamine release in this brain area, chronic nicotine use causes lower overall levels of dopamine in the nucleus accumbens, as the process of reuptake is accel-

erated to compensate for heightened dopamine release in the presence of nicotine (Ortelles and Barrantes, 890). This contributes to the depressive symptoms associated with withdrawal, as an imbalance in dopamine levels is a primary cause of depression. The implications of the various dopamine pathways' involvement in drug addiction are critical to the perceived need to consume nicotine. The way in which one experiences a reward for fulfilling an appetite for food parallels the way a dependent individual experiences a reward for fulfilling a craving for nicotine, as the rewarding aspects of both behaviors stem from the same system. Nicotine's ability to essentially hijack and rewire an individual's behavioral motivation system is central to its addictive qualities. Through the modification of dopamine pathways, there is yet another prevalent, structural factor contributing to nicotine dependence.

As discussed earlier, upregulation and desensitization are central to the experience of nicotine's withdrawal symptoms. One may expect that the effects of desensitization would eventually leave one's nAChRs wholly unresponsive to stimulation, negating the condition of nicotine dependence. However, this is clearly not the case since those experiencing nicotine dependence would eventually reach such a point of dependency that the addiction would not progress further. NACHRs on dopaminergic neurons are not fully desensitized by nicotine, allowing their continued activation from the consumption of nicotine (Ortelles and Barrantes, 887). Additionally, nicotine can indirectly stimulate dopamine release in the ventral tegmental area, another area critical to reward processing, through the  $\alpha 7$  subtype of nAChRs. This particular subtype of receptor is less affected by upregulation and desensitization (Ortelles and Barrantes, 888). The resistance to upregulation and desensitization, along with dopaminergic neurons' resistance to desensitization, allots two mechanisms through which nicotine can continue to stimulate dopamine release even after the brain has begun to develop a tolerance to the chemical. Continuous dopamine release as a result of nicotine prevents progressive tolerance from breaking the association between nicotine consumption and a chemical reward. At their root, these mechanisms represent another means through which maladaptive brain structure holds influence over behaviors associated with drug addiction. Even considering all of the preceding support for the supposition that addiction is a result of maladaptive brain structure, it is still important to consider some dissenting perspectives.

As with any field of study, there exists a variety of viewpoints that lend themselves to questioning the validity of research findings, and biopsychology is no exception. A necessary, but strikingly limiting factor in psychological research, is the ethical concerns about how research is conducted. These concerns prevent a vast array of research on human subjects from being conducted, even under the pretense that these subjects are selected on a volunteer basis. As such, research on the effects of drugs and their addictive potential is conducted on creatures of a lower trophic level, generally rats because of their relatively short lifespan. This relatively short life span allows for much more productive genetic research, as the effects of heredity are seen within a period of a few years. However, the complications of using animals for these types of research procedures are presented when one considers the concept of self-administration, something critical to drug addiction. Studies done on non-human animals related to addiction lack a component of self-administration, as these animals are not consciously aware of the substances they are made to consume (Kalant, 781). This may call into question the findings of research conducted in this manner, as generalizing knowledge ascertained from animal studies to human biological structures could be considered extrapolative. Considering that much of the research on structural adaptations of the brain during drug addiction involve non-human animal subjects, this is certainly a troubling predicament.

Methodology aside, when examining the findings themselves, more problems with our understanding become apparent. The human nervous system is incredibly complex; it acts comparably to our own global economic system, in that it is an interwoven web of activity that is inseparable from itself. One structure's activity could not exist without the activity of the other's, and herein lies the issue at hand. The changes related to drug addiction affect so many different brain structures and neurotransmitters that drawing specific conclusions can quickly err into the realm of generalizations and simplification. Take dopamine as an example, which has long been heralded as a neurotransmitter integrally connected to reward experience. In some studies, dopamine has been shown to not be directly connected to the experience of reward, but to exposure to novel stimuli. Rather, the reward experience is a result of the action of a variety of neurotransmitters, neuromodulators, and other factors (Kalant, 783). With the connection between dopamine and reward undermined, it is easy to

see how much of the research surrounding addiction can be refuted, or perceived as correlational data. Problems of this nature also surround genetic research on drug addiction. Genes shown to be connected to drug addiction are also associated with a large number of other responses to stimuli, weakening the connection between gene and behavior to a correlation (Kalant, 783). While correlational evidence still implies a connection, any mass of correlations does not equate to causation. However, despite these discrepancies, the correlational and practical support for drug addiction having a considerable structural basis remains.

The behaviors common to drug addiction in humans represent an incredibly prevalent transgression against our capacity for rational thought. In most other circumstances where an individual's long-term health is brought into question, the course of action is clear: eliminate the aversive stimulus. With drug addiction, while the correct course of action may be known, ceasing the health-damaging behaviors can be insurmountably difficult. The difficulty with this demonstrates some alteration of the system that decisions stem from the brain. Working from the supposition that nicotine addiction is the result of maladaptive brain structure could open the pathway to more effective treatments for addiction. For a treatment to be effective, it is critical to understand what specifically causes the ailment. Perhaps future approaches to the treatment of nicotine addiction could center on the processes of upregulation and desensitization, thereby alleviating withdrawal symptoms associated with cessation. If effective treatments for this condition could be properly implemented, a huge number of premature deaths could be prevented and the quality of life of many would be vastly improved.



*Works Cited*

- Biliński, Przemysław, Andrzej Wojtyła, Lucyna Kapka-Skrzypczak, Roman Chwedorowicz, Małgorzata Cyranka and Tadeusz Studziński. "Epigenetic regulation in drug addiction." *Annals of Agricultural and Environmental Medicine*. 19.3 (2012): 491-496. Web.
- Govind, Anitha. Paul Vezina, and William Green. "Nicotine-induced upregulation of nicotinic receptors: Underlying mechanisms and relevance to nicotine addiction." *Biochemical Pharmacology*. 78 (2009): 756-775. Science Direct. Web.
- Kalant, Harold. "What neurobiology cannot tell us about addiction." *Addiction*. 105. (2009): 780-789. Web.
- Maze, Ian, and Eric Nestler. "The epigenetic landscape of addiction." *Annals of the New York Academy of Sciences*. Vol.1216 Issue: Addiction Reviews. (2011): 99-113. Web.
- Miller, Rachel and Shuk-mei Ho. "Environmental epigenetics and asthma." *American Journal of Respiratory and Critical Care Medicine*. 177.6 (2008): 567-573. Web.
- Ortells, Marcello and Georgina Barrantes. "Tobacco dependence: A biochemical model of nicotine dependence." *Medical Hypotheses*. 74 (2010): 884-894. Web.
- Rahman, Shafiqur. "Brain nicotinic receptors as emerging targets for drug addiction: Neurobiology to translational research." *National Center for Biotechnology Information*. (2011): 339-365. Web.
- Renthal, William and Eric Nestler. "Epigenetic Mechanisms in Drug Addiction." *National Institutes of Health*. 14.8 (2009): 341-350. Web.

- Robison, Alfred and Eric Nestler. "Transcriptional and epigenetic mechanisms of addiction." *Nature Reviews: Neuroscience*. 12 (2011): 623-637. Web.
- Sweitzer, Maggie, Erik Donny, and Ahmad Hariri. "Imaging genetics and the neurobiological basis of individual differences in vulnerability to addiction." *Drug and Alcohol Dependence*. 123.1 (2012): 59-71. Science Direct. Web.
- Wang, Ke-Sheng, Xuefeng Liu, Qunyuan Zhang, and Min Zeng. "ANAPC1 and SLCO3A1 are associated with nicotine dependence: Meta-analysis of genome-wide association studies." *Drug and Alcohol Dependence*. 124.3 (2012): 325-332. Science Direct. Web.
- Wong, Chloe, Jonathan Mill, and Cathy Fernandes. "Drugs and addiction: An introduction to epigenetics." *Addiction*. 106 (2010): 480-489. Web.